REMARKS

Claims 4-8 are pending. Claims 1-3 were cancelled in responses to previous office communications, but are reiterated herein as required by the "Revised Amendment Practice", effective date July 30, 2003.

As a preliminary matter, claims 4-7 are objected to because "A" should have been "The" for all dependent claims. Claims 4-7 have been amended to recite "The" instead of "A". Applicant respectfully requests withdrawal of the objection.

Claim 8 is objected to because PMBCs" should have been PBMCs". Claim 8 has been amended to recite "PBMCs". Applicant respectfully requests withdrawal of the objection.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 4-8 are rejected under 35 U.S.C. § 112, first paragraph for reciting "PMBCs". Claims 4-8 have been amended to recite "PBMCs". Applicant respectfully requests withdrawal of the rejection.

Horwitz is not a proper prior art reference under § 103(a)

For the reasons discussed in the response to the Final Office Action dated August 27, 2002, Applicant maintains that the present invention is patently distinguishable over Horwitz in combination with the various secondary references. However, Horwitz is not a prior art reference. Horwitz was published September 30, 1999. The present application claims the benefit of the filing date under 35 U.S.C. § 119(e) of Serial Number 60, 196,446, filed April 11,

2000. The pending claims are fully supported by that application. Since Horwitz was published less than one year prior to the effective filing date in the present application, it is only available as prior art under 35 U.S.C. § 102(a) for use in the 35 U.S.C. § 103(a) rejection.

However, Horwitz is only prior art under § 102(a) if it is by "another". As indicated in the enclosed declaration of Dr. David Horwitz, he is the inventor of the present subject matter and the inventor/author of WO 99/48524 (i.e. Horwitz). Horwitz is therefore not prior art against the claims of the present application under § 102(a), and therefore, is not available as a reference under § 103(a).

Rejection of Claims 8, 5, and 7 under 35 U.S.C. § 103(a)

Claims 8, 5 and 7 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentably obvious over WO 99/48524 (Horwitz) in view of Rosario et al., 1999, Blood, 93:3558-3564, and Garderet et al., 1999, Transplantation, 67:124-130. As discussed above, Horwitz is not a proper prior art reference under 35 U.S.C. § 103(a). As regards the remaining references, Applicant submits that the Patent Office has failed to establish a *prima facie* case of obviousness.

Rosario et al., 1999, Blood, 93: 3558-3564, teach a method of ultraviolet B-irradiation of leukocytes to reduce the severity of GVHD. There is no teaching or disclosure in Rosario regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

Garderet et al., 1999, Transplantation, 67: 124-130, teach a method for separating reactive donor T cells from non-reactive donor T cells to reduce the risk of GVHD. There is no

teaching or disclosure in Garderet regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

As mentioned above, all of the pending rejected amended claims require contacting PBMC obtained from a recipient with a regulatory composition comprising TGF-β. Both the Rosario and Garderet references are silent in this regard; they do not teach or suggest contacting recipient PBMC with a regulatory composition comprising TGF-β as a means for preventing the rejection of a solid organ transplant. This deficiency is fatal to the rejection. Accordingly, *prima facie* obviousness is not established and the rejection of Claims 8, 5, and 7 under 35 U.S.C. § 103(a) should be withdrawn.

Rejection of Claim 4 under 35 U.S.C. § 103(a)

Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Horwitz in view in view of Rosario et al., 1999, Blood, 93:3558-3564, and Garderet et al. and further in view of Boning et al, 1998, Scand J. Immunol., 50: 612-618, or Dooms et al, 1998, Cytokine Network 9: 169. As discussed above, Horwitz is not a proper prior art reference under 35 U.S.C. § 103(a). As regards the remaining references, Applicant submits that the Patent Office has failed to establish a *prima facie* case of obviousness.

The present invention, Rosario and Garderet have been discussed above.

Bonig et al., teach methods of overcoming the immunosuppressive effects of TFG-β produced by tumors using cytokines. Thus, the methods taught by Bonig et al., are directed

toward using cytokines as means of stimulating the immune response against tumors by neutralizing the effect of immunosuppressive mediators, such as TGF-β. There is no teaching or disclosure in Bonig regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

Dooms et al., describe the effects of IL-2 and IL-15 on T cell survival and proliferation. Specifically, Dooms et al., teach that treatment of T cells with IL-2 sensitizes the treated T cells to Fas/Apo-induced cell death, whereas treatment of T cells with IL-15 results in T cell survival, but not cell proliferation. There is no teaching or disclosure in Dooms regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

As discussed above, all of the pending rejected amended claims require contacting PBMC obtained from a recipient with a regulatory composition comprising TGF-β. Both the Bonig and Dooms references are silent in this regard; they do not teach or suggest contacting recipient PBMC with a regulatory composition comprising TGF-β as a means for preventing the rejection of a solid organ transplant. This deficiency is fatal to the rejection. Accordingly, *prima facie* obviousness is not established and the rejection of Claim 4 under 35 U.S.C. § 103(a) should be withdrawn.

Rejection of Claim 6 under 35 U.S.C. § 103(a)

Claim 6 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Horwitz in view in view of Rosario et al., 1999, Blood, 93:3558-3564, and Garderet et al. and further in view of

Early et al., 1999, Clin. Exp. Immunol., 116: 527-33, Heitger et al., 1997, Blood, 90: 850-57, and Chen et al., 1998, J. Immunology, 161:909-918. As discussed above, Horwitz is not a proper prior art reference under 35 U.S.C. § 103(a). As regards the remaining references, Applicant submits that the Patent Office has failed to establish a *prima facie* case of obviousness.

The present invention, Rosario and Garderet have been discussed above.

The Patent Office states that Early et al teach a method of enriching for naïve CD$+ T cells for reducing the incidence of GVHD. There is no teaching or disclosure in Early regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

Heitger et al., teach methods for studying the role of the thymus in the human regeneration of CD4+/CD45RA+ and CD8+/CD45RA+ T cells following bone marrow transplant in humans. There is no teaching or disclosure in Heitger regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

Chen et al., teach methods for examining donor T cell immunity to host hemopoietic differentiation antigens as a possible means for using donor T cell responses to host hemopoietic differentiation antigens to eliminate residual host leukemia following bone marrow transplant. There is no teaching or disclosure in Chen regarding the use of a regulatory composition comprising TGF-β to induce a population of recipient suppressor T cells to prevent the rejection of a solid organ transplant.

As discussed above, all of the pending rejected amended claims require contacting PBMC obtained from a recipient with a regulatory composition comprising TGF-β as a means for preventing the rejection of a solid organ transplant. The Early, Heitger and Chen references are silent in this regard; they do not teach or suggest contacting PBMC with a regulatory composition comprising TGF-β they do not teach or suggest contacting recipient PBMC with a regulatory composition comprising TGF-β as a means for preventing the rejection of a solid organ transplant. This deficiency is fatal to the rejection. Accordingly, *prima facie* obviousness is not established and the rejection of Claim 6 under 35 U.S.C. § 103(a) should be withdrawn.

Please direct further questions in connection with this Application to the undersigned at (415) 781-1989.

Respectfully submitted,

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